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EDITORIAL COMMENT

Acute Adverse Reactions to Gadolinium in CMR

"Gadol" News!*

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In 1794, Johan Gadolin, a Finnish scientist, isolated a new rare earth metal from a black, heavy mineral found at a quarry on an island near Stockholm. Originally named ytterbia, in honor of the nearby village, the substance soon acquired the name gadolinite in honor of Johan, and subsequently gadolinium. Gadolin's surname, the Hebrew word for "great," was chosen from the Bible by his grandfather, a Lutheran minister (1). Although the paramagnetic properties of gadolinium have proven it to be a "great" discovery for biomedical imaging, free gadolinium is highly toxic and insoluble in water. As such, it must be chelated for clinical use, with macrocyclic chelates being more stable than linear chelates. Both variants are excreted unchanged in the urine. Despite its renal clearance, for over a decade, gadolinium was the preferred angiographic contrast agent for patients with severe renal dysfunction (2–4). That changed when gadolinium administration was linked to nephrogenic sclerosing fibrosis, a debilitating and sometimes fatal, multisystem fibrosing disorder seen only in patients with severe acute and chronic renal failure. This association led the U.S. Food and Drug Administration to issue a black box warning for gadolinium compounds in 2006 (5).

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For over a decade, gadolinium-based contrast agents have been approved by the U.S. Food and Drug Administration for use with magnetic resonance imaging to visualize lesions with abnormal vascularity in the brain and associated tissues, head and neck, and body (6), with an estimated >45 million doses administered in 101 countries (7). Despite obvious passage of the agent through the heart during intravenous administration for approved indications, gadolinium-based contrast agents remain unapproved for cardiac applications. Today, there is widespread "off-label" use of gadolinium in cardiac magnetic resonance (CMR), primarily with first-pass myocardial rest and stress perfusion and late gadolinium enhancement to identify fibrosis and inflammation (7). At our institution, the vast majority (>85%) of CMR studies include gadolinium contrast. Even though the majority of CMR studies in the literature focus on the diagnostic or prognostic utility of enhancement following gadolinium administration, little is known regarding its safety profile when used in this manner.

In this issue of *iJACC*, Bruder et al. (8) partially address the deficit in our knowledge regarding acute toxicity of gadolinium CMR. These investigators examined the EuroCMR (European Cardiovascular Magnetic Resonance) registry, a voluntary registry dataset of over 19,000 clinical CMR studies performed at 45 European institutions from April 2007 to March 2011. As has been our experience, the vast majority (90%) of CMR studies employed gadolinium. The 3 leading indications for CMR, comprising nearly 80% of studies, were: 1) evaluation of cardiomyopathy; 2) risk stratification of coronary artery disease (CAD); and 3) viability assessment (9). Despite nearly 18,000 doses, only 30 (0.17%) acute adverse reactions were reported (Table 1), all of which were classified as mild, with an incidence of 0.06% (gadoteridol and gadodiamid) to 0.47% (gadobenat). The most common acute adverse reactions were rash/hives, nausea, and anxiety. No moderate or severe

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reactions were reported; although some might consider rash/hives as a "moderate" reaction, Bruder et al. (8) used the American College of Radiology classification system of severity and manifestations of adverse reactions to contrast media (10). An interesting finding was the variability in event rates among indications for CMR—with patients being risk stratified for CAD having the lowest acute reaction rate (0.10%) as compared with a 0.42% acute adverse reaction rate in viability studies performed in patients with known CAD. The reason for this disparity likely has no meaningful clinical importance, but has also been noted in patients given iodinated contrast (10).

As might be expected, because the doses and route of administration are similar to that employed with gadolinium magnetic resonance imaging of other parts of the body, the very low acute event rate is within the 0.07% to 2.4% acute event rate noted in the general magnetic resonance literature, with comparable events including headache, nausea, and coldness at the injection site (7,10). Moderate and severe reactions are exceedingly rare. One series of over 687,000 doses reported only 5 severe reactions (~1 of 137,000) including periorbital edema, severe chest tightness, tongue swelling, and respiratory distress (11). The absence of these toxicities in only 18,000 doses is thus not surprising.

We applaud the European Society of Cardiology Cardiac MR Working Group's foresight in creating the EuroCMR registry, with internal review and auditing processes for all centers that perform CMR in an effort to ensure homogeneity and honesty in reporting. As highlighted by the investigators, registry data are inferior to a prospective randomized trial, but are more reflective of "real-world" experience than the highly selected population of a randomized controlled trial. The mean dose of gadolinium was 25.6 ml (0.128 mmol/kg) with a range of 0.012 to 0.3 mmol/kg. Although no relationship between the dose administered and acute reactions was noted, data were not collected regarding the administration rate, which may have an impact on acute toxicity. Importantly, left unknown are data regarding intermediate- and long-term toxicity of gadolinium-based contrast agents in the cardiac population. By their definition, acute reactions are those that occur within 60 min of contrast administration. Intermediate complications, such as thrombophlebitis or delayed allergic reactions, are also important to track. Unfortunately, the EuroCMR registry does not mandate intermediate or late follow-up for all patients (only for patients enrolled in specific CAD and hypertrophic cardiomyopathy protocols), and long-term complications, such as nephrogenic sclerosing fibrosis, are also potentially missed (Table 2) (12). Just as a different event rate was noted between patients being screened for CAD and patients with known CAD, a similar discrepancy could exist for other complications such as nephrogenic sclerosing fibrosis despite rigorous monitoring of renal function, which would be important to track.

Table 1. Reported Side Effects

Nausea
Vomiting
Warmth
Headache
Dizziness
Altered taste
Itching
Flushing
Chills
Sweats
Rash/hives
Swelling of eyes/face
Anxiety

Table 2. EuroCMR Electronic Case Record Form to Report Complications

Major complications: death, ventricular fibrillation, sustained ventricular tachycardia, cardiac arrest, allergic shock
Minor complications: allergy to contrast agent (other than shock), angina pectoris, dyspnea, nonsustained ventricular tachycardia, paroxysmal atrial fibrillation, severe increase in blood pressure with dobutamine stress, severe decrease in systolic blood pressure with dobutamine stress, bronchospasm with adenosine perfusion, second- or third-degree atrioventricular block, nausea, local complications at the intravenous infusion site, claustrophobia

While these data confirm the expected safety profile for the use of gadolinium contrast in CMR based on radiology applications, they can also be seen as a call for the creation of a CMR registry in the United States or an expanded "worldwide" CMR registry, perhaps under the umbrella of the Society for Cardiovascular Magnetic Resonance. Such an effort would enable monitoring of indications for CMR, use of and reactions to contrast agents, as well as adherence to appropriateness criteria. The registry may also serve as a platform for cost-effective analyses of the downstream testing impact of CMR. In an era of an increased awareness of the rising cost of health care and diminishing reimbursement, we should be proactive and use such a registry to track these areas in an effort to provide "gadolin" care to our patients.

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